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NEWS	3	NOV	26	MARPAT enhanced with FSORT command
NEWS	4	NOV	26	CHEMSAFE now available on STN Easy
NEWS	5	NOV	26	Two new SET commands increase convenience of STN searching
NEWS	6	DEC	01	ChemPort single article sales feature unavailable
NEWS	7	DEC	12	GBFULL now offers single source for full-text coverage of complete UK patent families
NEWS	8	DEC	17	Fifty-one pharmaceutical ingredients added to PS
NEWS	9	JAN	06	The retention policy for unread STNmail messages will change in 2009 for STN-Columbus and STN-Tokyo
NEWS	10	JAN	07	WPIDS, WPINDEX, and WPIX enhanced Japanese Patent Classification Data
NEWS	11	FEB	02	Simultaneous left and right truncation (SLART) added for CERAB, COMPUAB, ELCOM, and SOLIDSTATE
NEWS	12	FEB	02	GENBANK enhanced with SET PLURALS and SET SPELLING
NEWS	13	FEB	06	Patent sequence location (PSL) data added to USGENE
NEWS	14	FEB	10	COMPENDEX reloaded and enhanced
NEWS	15	FEB	11	WTEXTILES reloaded and enhanced
NEWS	16	FEB	19	New patent-examiner citations in 300,000 CA/CAPLUS patent records provide insights into related prior art
NEWS	17	FEB	19	Increase the precision of your patent queries -- use terms from the IPC Thesaurus, Version 2009.01
NEWS	18	FEB	23	Several formats for image display and print options discontinued in USPATFULL and USPAT2
NEWS	19	FEB	23	MEDLINE now offers more precise author group fields and 2009 MeSH terms
NEWS	20	FEB	23	TOXCENTER updates mirror those of MEDLINE - more precise author group fields and 2009 MeSH terms
NEWS	21	FEB	23	Three million new patent records blast AEROSPACE into STN patent clusters
NEWS	22	FEB	25	USGENE enhanced with patent family and legal status display data from INPADOCDB
NEWS	23	MAR	06	INPADOCDB and INPAFAMDB enhanced with new display formats
NEWS	24	MAR	11	EPFULL backfile enhanced with additional full-text applications and grants
NEWS	25	MAR	11	ESBIOBASE reloaded and enhanced
NEWS	26	MAR	20	CAS databases on STN enhanced with new super role for nanomaterial substances
NEWS	27	MAR	23	CA/CAPLUS enhanced with more than 250,000 patent equivalents from China

NEWS 28 MAR 30 IMSPATENTS reloaded and enhanced

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,  
AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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\* \* \* \* \* STN Columbus \* \* \* \* \*

FILE 'HOME' ENTERED AT 13:49:17 ON 31 MAR 2009

=> FIL REGISTRY

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FULL ESTIMATED COST	0.22	0.22

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DICTIONARY FILE UPDATES: 29 MAR 2009 HIGHEST RN 1129300-01-1

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=> E "5-CLDC"/CN 25

E1	1	5-CIS-SPIRILLOXANTHIN/CN
E2	1	5-CL-PADAB/CN
E3	0 -->	5-CLDC/CN
E4	1	5-CORRINCARBONITRILE, 1,2,3,24-TETRADEHYDRO-8,8,13,13,18,18,19-HEPTAMETHYL-, NICKEL COMPLEX/CN
E5	2	5-CORRINCARBONITRILE, 1,2,3,4-TETRADEHYDRO-4,21-DIHYDRO-8,8,13,13,18,18,19-HEPTAMETHYL-, COBALT COMPLEX/CN
E6	1	5-CORRINCARBONITRILE, 1,2-DIDEHYDRO-8,8,13,13,18,18,19-HEPTAMETHYL-, COBALT COMPLEX/CN

E7 1 5-CORRINCARBONITRILE,  
 1,2-DIDEHYDRO-8,8,13,13,18,18,19-HEPTAMETHYL-, NICKEL COMPLEX/CN  
 E8 1 5-CORRINCARBONITRILE, 1,8,8,13,13-PENTAMETHYL-/CN  
 E9 1 5-CORRINCARBONITRILE, 1,8,8,13,13-PENTAMETHYL-, NICKEL COMPLEX/CN  
 E10 1 5-CORRINCARBONITRILE, 1,8,8,13,13-PENTAMETHYL-, NICKEL COMPLEX,  
 (1R\*,19R\*)-/CN  
 E11 1 5-CORRINCARBONITRILE, 1,8,8,13,13-PENTAMETHYL-, NICKEL COMPLEX,  
 STEREOISOMER/CN  
 E12 2 5-CORRINCARBONITRILE, 1-FORMYL-8,8,13,13,18,18,19-HEPTAMETHYL-,  
 NICKEL COMPLEX, (1R\*,19R\*)-/CN  
 E13 1 5-CORRINCARBONITRILE,  
 2,3-DIDEHYDRO-8,8,13,13,18,18,19-HEPTAMETHYL-, NICKEL COMPLEX/CN  
 E14 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-/CN  
 E15 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-,  
 (1R,19R)-REL-/CN  
 E16 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-, COBALT  
 COMPLEX/CN  
 E17 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-,  
 MONOHYDROCHLORIDE/CN  
 E18 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-,  
 MONOHYDROCHLORIDE, (1R,19R)-REL-/CN  
 E19 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-,  
 MONOHYDROCHLORIDE, (1R,19R)-REL-, COMPD. WITH ETHANOL (1:1)/CN  
 E20 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-,  
 MONOHYDROCHLORIDE, TRANS-(±)-/CN  
 E21 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-,  
 MONOHYDROCHLORIDE, TRANS-(±)-, COMPD. WITH ETHANOL (1:1)/CN  
 E22 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-, NICKEL  
 COMPLEX, (1R\*,19R\*)-/CN  
 E23 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-, NICKEL  
 COMPLEX, TRANS-/CN  
 E24 2 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-, RHODIUM  
 COMPLEX/CN  
 E25 1 5-CORRINCARBONITRILE, 8,8,13,13,18,18,19-HEPTAMETHYL-, RHODIUM  
 COMPLEX, (1R\*,19R\*)-/CN

=> E "CLDC"/CN 25

E1 1 CLD 80/CN  
 E2 1 CLDADO/CN  
 E3 0 --> CLDC/CN  
 E4 1 CLDN1 PROTEIN (HUMAN CLONE DNA52185 GENE UNQ481)/CN  
 E5 1 CLDN10 PROTEIN (MOUSE STRAIN CZECH II CLONE IMAGE:3501011 GENE  
 CLDN10)/CN  
 E6 1 CLDN10 PROTEIN (MOUSE STRAIN FVB/N CLONE MGC:30291  
 IMAGE:5040100)/CN  
 E7 1 CLDN11 PROTEIN (HUMAN CLONE MGC:9232 IMAGE:3895040)/CN  
 E8 1 CLDN17 PROTEIN (HUMAN CLONE DNA73737 GENE UNQ758)/CN  
 E9 1 CLDN18 PROTEIN (HUMAN CLONE DNA73734 GENE UNQ778)/CN  
 E10 1 CLDN19 PROTEIN (HUMAN CLONE MGC:40523 IMAGE:5207628)/CN  
 E11 1 CLDN2 PROTEIN (HUMAN CLONE MGC:88250 IMAGE:30322852)/CN  
 E12 1 CLDN23 PROTEIN (HUMAN CLONE IMAGE:4639904 GENE CLDN23)/CN  
 E13 1 CLDN3 PROTEIN (MOUSE STRAIN FVB/N CLONE MGC:13769  
 IMAGE:4217040)/CN  
 E14 1 CLDN4L1 PROTEIN (XENOPUS LAEVIS CLONE MGC:81414 IMAGE:6635231  
 GENE CLDN4L1)/CN  
 E15 1 CLDN5-PROV PROTEIN (XENOPUS TROPICALIS CLONE MGC:89185  
 IMAGE:7016719 GENE CLDN5-PROV)/CN  
 E16 1 CLDN6 PROTEIN (HUMAN CLONE DNA73736 GENE UNQ757)/CN  
 E17 1 CLDN6-PROV PROTEIN (XENOPUS LAEVIS CLONE MGC:81720 IMAGE:6865216  
 GENE CLDN6-PROV)/CN  
 E18 1 CLDN7 PROTEIN (DANIO RERIO CLONE MGC:76832 IMAGE:6961476)/CN  
 E19 1 CLDN7 PROTEIN (DANIO RERIO STRAIN AB CLONE MGC:55228  
 IMAGE:3819607)/CN

E20	1	CLDN8 PROTEIN (HUMAN CLONE DNA73735 GENE UNQ779)/CN
E21	1	CLDN8 PROTEIN (HUMAN CLONE MGC:24067 IMAGE:4594155)/CN
E22	1	CLDNE PROTEIN (DANIO RERIO CLONE MGC:77738 IMAGE:7000808)/CN
E23	1	CLDNI PROTEIN (DANIO RERIO CLONE MGC:56243 IMAGE:5601526)/CN
E24	1	CLE 1000A/CN
E25	1	CLE 400/CN

=> E "5-CHLORO-2-DEOXYCYTIDINE"/CN 25

E1	1	5-CHLORO-2-CYCLOPROPYLPYRAZOLO(1,5-A)PYRIMIDINE/CN
E2	1	5-CHLORO-2-CYCLOPROPYLPYRIMIDINE/CN
E3	0 -->	5-CHLORO-2-DEOXYCYTIDINE/CN
E4	1	5-CHLORO-2-DICHLOROACETYLAMINO-O-CHLOROBENZOPHENONE/CN
E5	1	5-CHLORO-2-DICHLOROACETYLAMINO-O-METHYLBENZOPHENONE/CN
E6	1	5-CHLORO-2-DICHLOROACETYLAMINOBENZOPHENONE/CN
E7	1	5-CHLORO-2-DIFLUOROMETHOXYBENZALDEHYDE/CN
E8	1	5-CHLORO-2-DIMETHYLAMINO-3-METHYLBENZOXAZOLIUM IODIDE/CN
E9	1	5-CHLORO-2-DIMETHYLAMINOBENZOIC ACID METHYL ESTER/CN
E10	1	5-CHLORO-2-DODECYLOXYBENZENESULFONYL CHLORIDE/CN
E11	1	
5-CHLORO-2-ETHOXY-1-((2-(TRIMETHYLSILANYL)ETHOXY)METHYL)-1H-IMIDAZOLE-4-CARBOXALDEHYDE/CN		
E12	1	5-CHLORO-2-ETHOXY-4-METHOXYBENZENESULFONYL CHLORIDE/CN
E13	1	5-CHLORO-2-ETHOXYANILINE/CN
E14	1	5-CHLORO-2-ETHOXYBENZALDEHYDE/CN
E15	1	5-CHLORO-2-ETHOXYBENZAMIDE/CN
E16	1	5-CHLORO-2-ETHOXYBENZOIC ACID/CN
E17	1	5-CHLORO-2-ETHOXYBENZOTHAZOLE/CN
E18	1	5-CHLORO-2-ETHOXYBENZOYL CHLORIDE/CN
E19	1	5-CHLORO-2-ETHOXYCARBONYLINDOLE/CN
E20	1	5-CHLORO-2-ETHOXYCARBOXYLOXY-4-HYDROXYPYRIDINE/CN
E21	1	5-CHLORO-2-ETHOXYINDOLE/CN
E22	1	5-CHLORO-2-ETHOXYNICOTINIC ACID/CN
E23	1	5-CHLORO-2-ETHOXYPHENOL/CN
E24	1	5-CHLORO-2-ETHOXYPHENYLBORONIC ACID/CN
E25	1	5-CHLORO-2-ETHOXYPYRIDINE/CN

=> E "CHLORO-2-DEOXYCYTIDINE"/CN 25

E1	1	CHLORO-2-(PIPERIDIN-1-YL)ETHANE/CN
E2	1	CHLORO-2-(PYRROLIDIN-1-YL)ETHANE/CN
E3	0 -->	CHLORO-2-DEOXYCYTIDINE/CN
E4	1	CHLORO-2-FURYLDIMETHYLSILANE/CN
E5	1	CHLORO-2-FURYL METHYL ACETATE/CN
E6	1	CHLORO-2-HYDROXYPROPYL METHACRYLATE-DIETHYLENE GLYCOL DIMETHACRYLATE-METHYL METHACRYLATE COPOLYMER/CN
E7	1	CHLORO-2-NAPHTHYLMERCURY/CN
E8	1	CHLORO-2-NORBORNYLACETIC ANHYDRIDE/CN
E9	1	CHLORO-2-PENTENE/CN
E10	1	CHLORO-2-PHENYLPHENOL/CN
E11	1	CHLORO-2-PROPANONE/CN
E12	1	CHLORO-2-THIENYLCARBENE/CN
E13	1	CHLORO-2-THIENYLZINC/CN
E14	1	CHLORO-3,4-DIMETHOXYBENZOIC ACID METHYL ESTER/CN
E15	1	CHLORO-3-PYRIDYLDIAZIRINE/CN
E16	1	CHLORO-35CL-AMINE/CN
E17	1	CHLORO-35CL-AMINE-15N/CN
E18	1	CHLORO-35CL-AMINE-D/CN
E19	1	CHLORO-35CL-AMINE-D2/CN
E20	1	CHLORO-35CL-CHLORO-37CL-DIFLUOROMETHANE/CN
E21	1	CHLORO-35CL-METHYL METHYL ETHER/CN
E22	1	CHLORO-35CL-METHYL METHYL-13C ETHER/CN
E23	1	CHLORO-35CL-METHYL METHYL-D ETHER/CN
E24	1	CHLORO-35CL-METHYL-13C METHYL ETHER/CN

E25 1 CHLORO-35CL-METHYL-D METHYL ETHER/CN

=> E "5-CHLORO-2'-DEOXYCYTIDINE"/CN 25

E1 1 5-CHLORO-1H-PYRROLO(3,2-B)PYRIDINE/CN  
E2 1 5-CHLORO-2'-CHLORO-4'-NITROSALICYLANILIDE/CN  
E3 1 --> 5-CHLORO-2'-DEOXYCYTIDINE/CN  
E4 1 5-CHLORO-2'-DEOXYCYTIDINE-5'-TRIPHOSPHATE/CN  
E5 1 5-CHLORO-2'-DEOXYURIDINE/CN  
E6 1 5-CHLORO-2'-FLUORO-2-(2-HYDROXYETHYL)AMINOBENZOPHENONE/CN  
E7 1 5-CHLORO-2'-FLUORO-2-(HYDROXYMETHYL)BENZHYDROL/CN  
E8 1 5-CHLORO-2'-FLUORO-2-IODOBENZOPHENONE/CN  
E9 1 5-CHLORO-2'-O-METHYLANZIAIC ACID/CN  
E10 1 5-CHLORO-2(1H)-PYRIDINETHIONE/CN  
E11 1 5-CHLORO-2(1H)-PYRIDONE/CN  
E12 1 5-CHLORO-2(1H)-PYRIMIDINONE/CN  
E13 1 5-CHLORO-2(1H)-PYRIMIDINONE HYDROCHLORIDE/CN  
E14 1 5-CHLORO-2(1H)-PYRIMIDINONE POTASSIUM SALT/CN  
E15 1 5-CHLORO-2(3H)-BENZOFURANONE/CN  
E16 1 5-CHLORO-2(3H)-BENZOTHAIOLETHIONE/CN  
E17 1 5-CHLORO-2(3H)-BENZOXAZOLETHIONE/CN  
E18 1 5-CHLORO-2(3H)-BENZOXAZOLONE/CN  
E19 1 5-CHLORO-2(5H)-FURANONE/CN  
E20 1 5-CHLORO-2,1,3-BENZOSELENADIAZOLE/CN  
E21 1 5-CHLORO-2,1,3-BENZOTHIADIAZOLE/CN  
E22 1 5-CHLORO-2,1,3-BENZOXADIAZOLE/CN  
E23 1 5-CHLORO-2,1,3-BENZOXADIAZOLE-4-SULFONYL CHLORIDE/CN  
E24 1 5-CHLORO-2,1-BENZISOTHAIOLE/CN  
E25 1 5-CHLORO-2,1-BENZISOXAZOLE/CN

=> S E3

L1 1 "5-CHLORO-2'-DEOXYCYTIDINE"/CN

=> DIS L1 1 SQIDE

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN

RN 32387-56-7 REGISTRY

CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

OTHER NAMES:

CN 5-Chloro-2'-deoxycytidine

CN 5-Chlorodeoxycytidine

CN NSC 371331

FS STEREOSEARCH

MF C9 H12 Cl N3 O4

LC STN Files: BEILSTEIN\*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT,  
CHEMCATS, DDFU, DRUGU, EMBASE, IMSDRUGNEWS, IMSRESEARCH, MEDLINE,  
PROUSDDR, TOXCENTER, USPATFULL

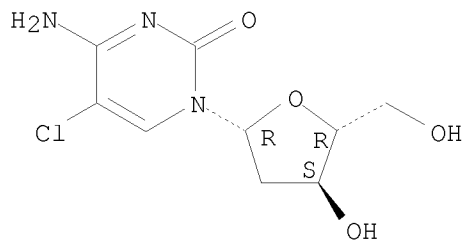
(\*File contains numerically searchable property data)

DT.CA CAPLUS document type: Conference; Dissertation; Journal; Patent

RL.P Roles from patents: BIOL (Biological study); PREP (Preparation); RACT  
(Reactant or reagent); USES (Uses)

RL.NP Roles from non-patents: ANST (Analytical study); BIOL (Biological  
study); FORM (Formation, nonpreparative); PREP (Preparation); PROC  
(Process); PRP (Properties); RACT (Reactant or reagent); USES (Uses)

Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

41 REFERENCES IN FILE CA (1907 TO DATE)  
41 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file medline caplus wpids uspatfull  
COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
8.84	9.06

FULL ESTIMATED COST

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=> s l1

L2 59 L1

=> s l2 and tetrahydrouridine

L3 26 L2 AND TETRAHYDROURIDINE

=> s l3 and radiation

L4 20 L3 AND RADIATION

=> d l4 1-20 ibib, abs, hitstr

L4 ANSWER 1 OF 20 MEDLINE on STN

ACCESSION NUMBER: 2001644763 MEDLINE

DOCUMENT NUMBER: PubMed ID: 11697326

TITLE: Five-chlorodeoxycytidine, a tumor-selective enzyme-driven radiosensitizer, effectively controls five advanced human tumors in nude mice.

AUTHOR: Greer S; Alvarez M; Mas M; Wozniak C; Arnold D; Knapinska A; Norris C; Burk R; Aller A; Dauphinee M

CORPORATE SOURCE: Department of Microbiology and Immunology, University of Miami School of Medicine, FL 33101, USA.

CONTRACT NUMBER: 1R41CA79272-01A (United States NCI NIH HHS)

SOURCE: International journal of radiation oncology, biology, physics, (2001 Nov 1) Vol. 51, No. 3, pp. 791-806.  
Journal code: 7603616. ISSN: 0360-3016.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200112  
ENTRY DATE: Entered STN: 8 Nov 2001  
Last Updated on STN: 23 Jan 2002  
Entered Medline: 4 Dec 2001

AB PURPOSE: The study's goals were as follows: (1) to extend our past findings with rodent tumors to human tumors in nude mice, (2) to determine if the drug protocol could be simplified so that only CldC and one modulator, tetrahydrouridine (H4U), would be sufficient to obtain efficacy, (3) to determine the levels of deoxycytidine kinase and dCMP deaminase in human tumors, compared to adjacent normal tissue, and (4) to determine the effect of CldC on normal tissue radiation damage to the cervical spinal cord of nude mice. METHODS AND MATERIALS: The five human tumors used were as follows: prostate tumors, PC-3 and H-1579; glioblastoma, SF-295; breast tumor, GI-101; and lung tumor, H-165. The duration of treatment was 3-5 weeks, with drugs administered on Days 1-4 and radiation on Days 3-5 of each week. The biomodulators of CldC were N-(Phosphonacetyl)-L-aspartate (PALA), an inhibitor of aspartyl transcarbamoylase, 5-fluorodeoxycytidine (FdC), resulting in tumor-directed inhibition of thymidylate synthetase, and H4U, an inhibitor of cytidine deaminase. The total dose of focused irradiation of the tumors was usually 45 Gy in 12 fractions. RESULTS: Marked radiosensitization was obtained with CldC and the three modulators. The average days in tumor regrowth delay for X-ray compared to drugs plus X-ray, respectively, were: PC-3 prostate, 42-97; H-1579 prostate, 29-115; glioblastoma, 5-51; breast, 50-80; lung, 32-123. Comparative studies with PC-3 and H-1579 using CldC coadministered with H4U, showed that both PALA and FdC are dispensable, and the protocol can be simplified with equal and possibly heightened efficacy. For example, PC-3 with X-ray and (1) no drugs, (2) CldC plus the three modulators, (3) a high dose of CldC, and (4) escalating doses of CldC resulted in 0/10, 3/9, 5/10, and 6/9 cures, respectively. The tumor regrowth delay data followed a similar pattern. After treating mice only 11/2 weeks with CldC + H4U, 92% of the PC-3 tumor cells were found to possess CldU in their DNA. The great majority of head-and-neck tumors from patient material had markedly higher levels of dC kinase and dCMP deaminase than found in adjacent normal tissue. Physiologic and histologic studies showed that CldC + H4U combined with X-ray, focused on the cervical spinal cord, did not result in damage to that tissue. CONCLUSIONS: 5-CldC coadministered with only H4U is an effective radiosensitizer of human tumors. Ninety-two percent of PC-3 tumor cells have been shown to take up ClUra derived from CldC in their DNA after only 11/2 weeks and 2 weeks of bolus i.p. injections. Enzymatic alterations that make tumors successful have been exploited for a therapeutic advantage. The great electronegativity, coupled with the relatively small Van der Waal radius of the Cl atom, may result in CldC's possessing the dual advantageous properties of FdC on one hand and BrdU and IdU on the other hand. These advantages include autoenhancing the incorporation of CldUTP into DNA by not only overrunning but also inhibiting the formation of competing TTP pools in tumors. A clinical trial is about to begin, with head-and-neck tumors as a first target of CldC radiosensitization.

L4 ANSWER 2 OF 20 MEDLINE on STN  
ACCESSION NUMBER: 1995332057 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 7607927  
TITLE: Five-chlorodeoxycytidine and biomodulators of its metabolism result in fifty to eighty percent cures of advanced EMT-6 tumors when used with fractionated

radiation.  
AUTHOR: Greer S; Schwade J; Marion H S  
CORPORATE SOURCE: Department of Microbiology and Immunology, University of  
Miami School of Medicine, FL 33101, USA.  
SOURCE: International journal of radiation oncology, biology,  
physics, (1995 Jul 15) Vol. 32, No. 4, pp. 1059-69.  
Journal code: 7603616. ISSN: 0360-3016.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 199508  
ENTRY DATE: Entered STN: 28 Aug 1995  
Last Updated on STN: 28 Aug 1995  
Entered Medline: 17 Aug 1995

AB PURPOSE: To extend our findings in previous radiation and  
biochemical studies with five rodent tumors, in which we used one and  
occasionally two or three irradiations. The extent of control of the  
EMT-6 mammary adenocarcinoma was determined using fractionated  
radiation (12 irradiations) over a 3-week period using the  
radiosensitizer 5-chloro-2'-deoxycytidine (CldC) and biomodulators of its  
metabolism: N-(Phosphonacetyl)-L-aspartate (PALA),  
tetrahydrouridine and 5-fluoro-2'-deoxycytidine (FdC). METHODS  
AND MATERIALS: Mammary adenocarcinoma EMT-6 tumors implanted 1 week prior  
to therapy in BALB/c mice were subjected to single daily doses of focused  
radiation, not exceeding a total of 60 Gy, on days 2-5 of each  
week. N-(Phosphonacetyl)-L-aspartate (PALA) was administered on the first  
day of therapy. Five-fluoro-2'-deoxycytidine and CldC were administered  
in the morning and afternoon, respectively, of the next 2 days, and CldC  
was administered on the fourth day. Tetrahydrouridine was  
always coadministered with FdC or CldC. Drug and radiation  
treatments overlapped for 3 weeks. RESULTS: Fifty to 80% cures (usually  
70%) were obtained with no apparent morbidity and the same moderate weight  
loss that occurs with radiation alone. Neither tumor regrowth  
delay nor cures were obtained with drugs or radiation alone. An  
apparent threefold dose increase effect was obtained with the end point:  
"days to reach 4 times initial tumor volume." Increasing the  
radiation dose threefold (without drugs) resulted in four out of  
five deaths; increasing the dose twofold (without drugs) resulted in  
extensive weight loss and hair loss in the entire ventral area and no  
cures. Increasing the dose of drugs or radiation 1.5-fold, in  
the complete protocol, did not result in increased morbidity. Comparative  
studies with Iododeoxyuridine demonstrate the heightened efficacy of CldC.  
CONCLUSIONS: One cannot achieve the same results obtained with CldC and  
the modulators by merely increasing the dose of radiation.  
There is a significant window of safety in this approach. The evidence we  
have obtained with EMT-6, the fifth rodent tumor we have studied with  
CldC, as well as the demonstrated and proposed reasons for its superior  
efficacy over 5-Iododeoxyuridine (and 5-Bromodeoxyuridine), drugs in  
current use, indicate that CldC will allow more aggressive treatment of  
human tumors with radiation than is now feasible.

L4 ANSWER 3 OF 20 MEDLINE on STN  
ACCESSION NUMBER: 1992138271 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 1735688  
TITLE: 5-chlorodeoxycytidine, a radiosensitizer effective against  
RIF-1 and Lewis lung carcinoma, is also effective against a  
DMBA-induced mammary adenocarcinoma and the EMT-6 tumor in  
BALB/c mice.  
AUTHOR: Greer S; Santos O; Gottlieb C; Schwade J; Marion H S  
CORPORATE SOURCE: Department of Microbiology and Immunology, University of



SOURCE: Miami School of Medicine, FL 33136.  
 International journal of radiation oncology, biology,  
 physics, (1992) Vol. 22, No. 3, pp. 505-10.  
 Journal code: 7603616. ISSN: 0360-3016.

PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199203  
 ENTRY DATE: Entered STN: 29 Mar 1992  
 Last Updated on STN: 29 Mar 1992  
 Entered Medline: 10 Mar 1992

AB 5-Chlorodeoxycytidine (CldC), coadministered with modulators of pyrimidine metabolism, is an effective radiosensitizer of murine tumors. Past studies that utilized RIF-1 tumors in C3H mice and Lewis lung carcinoma (LLC) in BDF1 mice have been extended with an emphasis on using multiple cycles of drug administration followed by irradiation of LLC and the use of two additional tumor models. Four of seven cures of BDF1 mice bearing LLC were obtained with three doses of 20 Gy irradiation, in which the first and third dose were preceded by a "Standard Protocol" that includes N-(phosphonacetyl)-L-aspartic acid (PALA), 5-fluorodeoxycytidine (FdC), tetrahydrouridine, and the radiosensitizer, 5-chlorodeoxycytidine. No cures were obtained in groups of mice receiving radiation alone or drugs alone, and there were no "no takes" in untreated control groups (six mice/group). Extensive tumor inhibition, exceeding that obtained with drugs or radiation alone, was obtained with two cycles of drugs and radiation combined when a dimethylbenzanthracene-induced mammary adenocarcinoma was used in BALB/c mice. With the EMT-6 tumor in BALB/c mice, doses of 10 and 20 Gy were administered 9 and 16 days after tumor implantation, each preceded with the Standard Protocol; this resulted in a tumor growth delay of 24 days. No tumor growth delay occurred with drugs or radiation alone. The omission of PALA, FdC or CldC from the Standard Protocol resulted in loss of tumor control, which was obtained with the complete protocol. The fact that 5-chlorodeoxycytidine is an effective radiosensitizer in four rodent tumor systems is compelling evidence that it has potential as a radiosensitizer of human tumors, especially in view of its tumor selectivity and its resistance to catabolism when used with modulators of its metabolism, and in view of the high levels of the key enzymes in human tumors, which can convert 5-chlorodeoxycytidine to 5-chlorodeoxyuridine triphosphate, the proximate radiosensitizer.

L4 ANSWER 4 OF 20 MEDLINE on STN  
 ACCESSION NUMBER: 1990368420 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 2394614  
 TITLE: Radiation, pool size and incorporation studies in mice with 5-chloro-2'-deoxycytidine.  
 AUTHOR: Santos O; Perez L M; Briggles T V; Boothman D A; Greer S B  
 CORPORATE SOURCE: Department of Microbiology and Immunology, University of Miami, School of Medicine, FL 33101.  
 CONTRACT NUMBER: CA 33219 (United States NCI NIH HHS)  
 CA 37791 (United States NCI NIH HHS)  
 SOURCE: International journal of radiation oncology, biology, physics, (1990 Aug) Vol. 19, No. 2, pp. 357-65.  
 Journal code: 7603616. ISSN: 0360-3016.

PUB. COUNTRY: United States  
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, NON-U.S. GOV'T)  
 (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)

LANGUAGE: English  
 FILE SEGMENT: Priority Journals

ENTRY MONTH: 199010  
ENTRY DATE: Entered STN: 9 Nov 1990  
Last Updated on STN: 9 Nov 1990  
Entered Medline: 11 Oct 1990

AB Bolus doses of 5-chlorodeoxycytidine (CldC) administered with modulators of pyrimidine metabolism, followed by X-irradiation, resulted in a 2-fold dose increase effect against RIF-1 tumors in C3H mice. Pool size studies of the fate of [14C]-CldC in BDF1 mice bearing Sarcoma-180 tumors, which demonstrated the rapid formation of 5-chlorodeoxycytidylate (CldCMP), and incorporation of CldC as such in RIF-1 tumor DNA, indicate that CldC is a substrate for deoxycytidine kinase, as our past Km studies have shown. Our data indicate that 5-chlorodeoxyuridine triphosphate (CldUTP) accumulates from both the cytidine deaminase-thymidine kinase pathway, as well as from the deoxycytidine kinase-dCMP deaminase pathway, in tumor tissue. As shown in a previous study, tetrahydrouridine (H4U), a potent inhibitor of cytidine deaminase, can effectively inhibit the enzyme in the normal tissues of BDF1 mice. When H4U was administered with the modulators N-(phosphonacetyl)-L-aspartic acid (PALA) and 5-fluorodeoxycytidine (FdC), the levels of CldC-derived RNA and DNA directed metabolites increased in tumor and decreased in normal tissues compared to when CldC was administered alone. These modulators inhibit the de novo pathway of thymidine biosynthesis, lowering thymidine triphosphate (TTP) levels, which compete with CldUTP for incorporation into DNA. 5-Benzylacetyluridine (BAU), an inhibitor of uridine phosphorylase, was also utilized. DNA incorporation studies using C3H mice bearing RIF-1 tumors showed that the extent of incorporation of 5-chlorodeoxyuridine (CldU) into DNA correlates with the levels of cytidine and dCMP deaminases; this is encouraging in view of their high activity in many human malignancies and the low activities in normal tissues, including those undergoing active replication. Up to 3.9% replacement of thymidine by CldU took place in RIF-1 tumors, whereas incorporation into bone marrow was below our limit of detection. CldC did not result in photosensitization under conditions in cell culture in which radiosensitization to X rays was obtained. Thus, the combination of CldC with modulators of its metabolism has potential as a modality of selective radiosensitization for ultimate clinical use in a wider range of tumors than those of the brain.

L4 ANSWER 5 OF 20 MEDLINE on STN  
ACCESSION NUMBER: 1989233931 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 2715074  
TITLE: Selective radiosensitization and cytotoxicity of human melanoma cells using halogenated deoxycytidines and tetrahydrouridine.  
AUTHOR: Lawrence T S; Davis M A  
CORPORATE SOURCE: Department of Radiation Oncology, University of Michigan, Ann Arbor 48109.  
SOURCE: International journal of radiation oncology, biology, physics, (1989 May) Vol. 16, No. 5, pp. 1243-6.  
Journal code: 7603616. ISSN: 0360-3016.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: (COMPARATIVE STUDY)  
(IN VITRO)  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198906  
ENTRY DATE: Entered STN: 6 Mar 1990  
Last Updated on STN: 3 Feb 1997  
Entered Medline: 19 Jun 1989

AB The halogenated pyrimidines 5-chloro-2'-deoxycytidine (CldCyd) and 5-bromo-2'-deoxycytidine (BrdCyd) can act as radiosensitizers and

cytotoxic agents. It was hypothesized that tumor cells and normal cells might use different metabolic pathways to incorporate these halogenated deoxycytidines into DNA. This difference could potentially be exploited to produce selective radiosensitization and cytotoxicity of human tumor cells compared to normal human fibroblasts. This hypothesis was tested using two human melanoma cell lines and two normal fibroblast cell lines. Either CldCyd or BrdCyd alone caused both cytotoxicity and radiosensitization of tumor and normal cells. The addition of the cytidine deaminase inhibitor tetrahydrouridine (H4U) significantly protected the normal cells but had relatively little effect on the tumor cells. These data indicate that it may be possible to exploit differences between the pyrimidine metabolism of normal cells and melanoma cells to improve the therapeutic index of halogenated pyrimidines both as radiosensitizers and as cytotoxic agents.

L4 ANSWER 6 OF 20 MEDLINE on STN  
 ACCESSION NUMBER: 1987007839 MEDLINE  
 DOCUMENT NUMBER: PubMed ID: 3759575  
 TITLE: Sensitization to X ray by 5-chloro-2'-deoxycytidine co-administered with tetrahydrouridine in several mammalian cell lines and studies of 2'-chloro derivatives.  
 AUTHOR: Perez L M; Greer S  
 CONTRACT NUMBER: CA33219 (United States NCI NIH HHS)  
 SOURCE: International journal of radiation oncology, biology, physics, (1986 Aug) Vol. 12, No. 8, pp. 1523-7. Journal code: 7603616. ISSN: 0360-3016.  
 PUB. COUNTRY: United States  
 DOCUMENT TYPE: (IN VITRO)  
 (JOURNAL; Article; (JOURNAL ARTICLE)  
 (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 198610  
 ENTRY DATE: Entered STN: 2 Mar 1990  
 Last Updated on STN: 3 Feb 1997  
 Entered Medline: 30 Oct 1986

AB 5-Chloro-2'-deoxycytidine (CldC) + tetrahydrouridine (H4U) sensitizes mammalian cells (HEp-2, RIF-1, S-180) to X ray. This sensitization, as demonstrated previously with HEp-2 cells, is heightened when cells are pre-incubated with inhibitors of pyrimidine synthesis. CHO cells, which intrinsically lack both cytidine deaminase (CD) and deoxycytidylate deaminase (dCMPD), are sensitized to X ray by 5-chlorodeoxyuridine (CldU) but display no significant sensitization with CldC + H4U. The presence and level of these deaminases appears to correlate with X ray sensitization in cell culture. From experiments in cell culture, it can be inferred that one pathway of conversion, deoxycytidine kinase----dCMPD, or CD----thymidine kinase, may be sufficient for metabolizing CldC to a radiosensitizer. However, if both pathways are blocked, as in CHO cells, no X ray sensitization results. In addition to HEp-2 cells, which are extremely elevated in both CD and dCMPD activities, we have examined the sensitization of S-180 and RIF-1 cells to X ray by CldC + H4U. Both cell lines possess an enzymatic profile consistent with their sensitization to X ray by CldC + H4U. Dose enhancement ratios of 1.5 to 1.9 for cells treated with CldC + H4U and ratios of 2.0-2.7 for cells pre-treated with inhibitors of pyrimidine synthesis prior to CldC + H4U have been obtained. Based on reports of the marked X ray sensitization of bacteria by 2'-chloro-2'-deoxythymidine, we obtained 2',5-dichloro-2'-deoxycytidine and 5-bromo-2'-chloro-2'-deoxyuridine and found these analogs to be X ray sensitizers of mammalian cells. The strategy that we propose with CldC + H4U and the related 2'-chloro derivatives, based on the elevation of CD and dCMPD in human tumors, offers a degree of selectivity that is not

necessarily related to differences in cell kinetics; such that malignancies other than brain tumors may be amenable to this therapy.

L4 ANSWER 7 OF 20 MEDLINE on STN  
ACCESSION NUMBER: 1986189633 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 3698014  
TITLE: In vitro and in vivo radiation sensitization by the halogenated pyrimidine 5-chloro-2'-deoxycytidine.  
AUTHOR: Russell K J; Rice G C; Brown J M  
CONTRACT NUMBER: 5 T32 CA 09302-07 (United States NCI NIH HHS)  
CA-15201 (United States NCI NIH HHS)  
SOURCE: Cancer research, (1986 Jun) Vol. 46, No. 6, pp. 2883-7.  
Journal code: 2984705R. ISSN: 0008-5472.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)  
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198606  
ENTRY DATE: Entered STN: 21 Mar 1990  
Last Updated on STN: 3 Feb 1997  
Entered Medline: 25 Jun 1986

AB 5-Chloro-2'-deoxycytidine (Cld/Cyd) is hypothesized to have preferential incorporation into tumor DNA on the basis of elevated deoxycytidine-5'-phosphate deaminase and deoxycytidine kinase levels in tumors. Radiosensitization by Cld/Cyd was evaluated in exponentially growing Chinese hamster ovary cells by determining the ratio of radiation doses in control and treated cells to produce the same degree of cell killing (sensitizer enhancement ratio). Sensitizer enhancement ratios of 1.2-1.8 are seen at Cld/Cyd concentrations of 3-100 microM, 64 h incubation, and 200-600 cGy irradiation. Coincubation with tetrahydrouridine (H4Urd), a proposed inhibitor of Cld/Cyd catabolism by plasma cytidine deaminase resulted in no enhanced drug or radiation cytotoxicity. C3H mice given implants of RIF-1 tumors received 72-h continuous i.p. infusions of Cld/Cyd with or without H4Urd, or 5-bromo-2'-deoxyuridine (BrdUrd). Excised tumors were irradiated as single cell suspensions in vitro. Infusions of equimolar (0.4 mmol/kg/day) Cld/Cyd or BrdUrd resulted in greater radiosensitization by BrdUrd with no potentiation of Cld/Cyd by coinfusion with 0.8 mmol/kg/day H4Urd. Infusions with equitoxic doses of Cld/Cyd (0.8 mmol/kg/day) or BrdUrd (0.4 mmol/kg/day) yielded equal BrdUrd and Cld/Cyd sensitizer enhancement ratios of 1.6, without H4Urd potentiation of Cld/Cyd. Fluorescence-activated cell sorter analysis of tumor cell suspensions using a monoclonal antibody reactive with BrdUrd and Cld/Cyd disclosed a population of noncycling cells in tumors treated with Cld/Cyd/H4Urd that is not seen in tumors exposed to either BrdUrd or Cld/Cyd alone.

L4 ANSWER 8 OF 20 MEDLINE on STN  
ACCESSION NUMBER: 1984288944 MEDLINE  
DOCUMENT NUMBER: PubMed ID: 6236189  
TITLE: Marked radiosensitization of cells in culture to X ray by 5-chlorodeoxycytidine coadministered with tetrahydrouridine, and inhibitors of pyrimidine biosynthesis.  
AUTHOR: Perez L M; Mekras J A; Briggles T V; Greer S  
SOURCE: International journal of radiation oncology, biology, physics, (1984 Aug) Vol. 10, No. 8, pp. 1453-8.  
Journal code: 7603616. ISSN: 0360-3016.  
PUB. COUNTRY: United States  
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)  
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 198410  
ENTRY DATE: Entered STN: 20 Mar 1990  
Last Updated on STN: 20 Mar 1990  
Entered Medline: 24 Oct 1984

AB Our approach to overcome the problem of rapid catabolism and general toxicity encountered with 5-halogenated analogues of deoxyuridine (5-bromo, chloro or iododeoxyuridine), which has limited their use as tumor radiosensitizers, is to utilize 5-chlorodeoxycytidine (CldC) with tetrahydrouridine (H4U). We propose that CldC, coadministered with H4U, is metabolized in the following manner:  
CldC----CldCMP----CldUMP---- ----CldUTP----DNA. All the enzymes of this pathway are elevated in many human malignant tumors and in HEP-2 cells. In X irradiation studies with HEP-2 cells, limited to 1 or 2 radiation doses, we have obtained 3.0 to 3.8 apparent dose enhancement ratios (these represent upper limits) when cells are preincubated with inhibitors of pyrimidine biosynthesis: N-(Phosphonacetyl)-L-aspartate (PALA) and 5-fluorodeoxyuridine (FdU) or 5-fluorodeoxycytidine (FdC) + H4U. Optimum conditions for radiosensitization are: PALA (0.1 mg/ml) 18-20 hr prior to FdU (0.1 microM) or FdC (0.02 microM) + H4U (0.1 mM) followed 6 hr later by CldC (0.1-0.2 mM) + H4U (0.1 mM) for 56-68 hr. Viabilities of 10 +/- 4% to 15 +/- 1% (+/- S.E.) were obtained for drug-treated unirradiated cells. Enzymatic studies indicate that this toxicity may be tumor selective. CldC + H4U alone (at these concentrations) results in 20% substitution of CldU for thymidine in DNA (determined by HPLC analysis). Preliminary toxicity studies indicate that mice will tolerate treatment protocols involving a single dose of PALA (200 mg/kg) followed by a dose of FdU (50 mg/kg) and 3 cycles of CldC (500 mg/kg) + H4U (100 mg/kg) at 10 hour intervals, with marginal weight loss (4%). In this approach we seek to obtain preferential conversion of CldC to CldUTP at the tumor site by taking advantage of quantitative differences in enzyme levels between tumors and normal tissues.

L4 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2008:857776 CAPLUS  
DOCUMENT NUMBER: 149:167941  
TITLE: Designer therapy of pancreatic tumors  
INVENTOR(S): Greer, Sheldon B.  
PATENT ASSIGNEE(S): University of Miami, USA  
SOURCE: PCT Int. Appl., 56pp.  
CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2008085611	A2	20080717	WO 2007-US85613	20071127
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW:	AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,			

BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.:

US 2006-861088P

P 20061127

AB Chemotherapeutic and Radiation sensitizing agents which target tumor cells, specifically, based on the elevation of enzyme pathways, provide highly selective drug therapy. These agents are combined with modulating doses of cytidine deaminase inhibitors to increase selectivity. Furthermore, high doses of these cytidine deaminase inhibitors have the potential of counteracting the aggressive and metastatic characteristics of pancreatic tumors. For tumors with high levels of cytidine deaminase, such as pancreatic tumors, this elevation provides a therapeutic approach with prodrugs that require deamination for their activation. For tumors with high levels of uridine/cytidine kinase, a different class of pyrimidine analogs can be activated selectively in tumors for a therapeutic advantage.

IT 32387-56-7, 5-Chlorodeoxycytidine

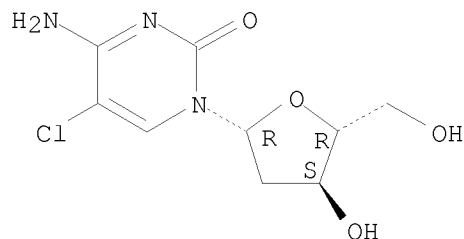
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(designer therapy of pancreatic tumors using chemotherapeutic and radiosensitizer agents and cytidine deaminase inhibitors in relation to uridine/cytidine kinase)

RN 32387-56-7 CAPLUS

CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2001:738057 CAPLUS

DOCUMENT NUMBER: 137:17179

TITLE: 5-chlorodeoxycytidine, a tumor-selective enzyme-driven radiosensitizer, effectively controls five advanced human tumors in nude mice

AUTHOR(S): Greer, S.; Alvarez, M.; Mas, M.; Wozniak, C.; Arnold, D.; Knapinska, A.; Norris, C.; Burk, R.; Aller, A.; Dauphinee, M.

CORPORATE SOURCE: Departments of Microbiology and Immunology, Biochemistry and Molecular Biology, Radiation Oncology, Sylvester Cancer Center, University of Miami School of Medicine, Miami, FL, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (2001), 51(3), 791-806  
CODEN: IOBPD3; ISSN: 0360-3016

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Purpose: The study goals were as follows: (1) to extend our past findings with rodent tumors to human tumors in nude mice, (2) to determine if the drug protocol could be simplified so that only CldC and one modulator, tetrahydrouridine (H4U), would be sufficient to obtain efficacy, (3) to determine the levels of deoxycytidine kinase and dCMP deaminase in human tumors, compared to adjacent normal tissue, and (4) to determine the effect of CldC on normal tissue radiation damage to the cervical spinal

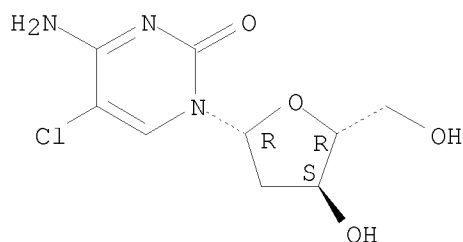
cord of nude mice. Methods and Materials: The five human tumors used were as follows: prostate tumors, PC-3 and H-1579; glioblastoma, SF-295; breast tumor, GI-101; and lung tumor, H-165. The duration of treatment was 3-5 wk, with drugs administered on Days 1-4 and radiation on Days 3-5 of each week. The biomodulators of CldC were N-(Phosphonacetyl)-L-aspartate (PALA), an inhibitor of aspartyl transcarbamoylase, 5-fluorodeoxycytidine (FdC), resulting in tumor-directed inhibition of thymidylate synthetase, and H4U, an inhibitor of cytidine deaminase. The total dose of focused irradiation of the tumors was usually 45 Gy in 12 fractions. Results: Marked radiosensitization was obtained with CldC and the three modulators. The average days in tumor regrowth delay for X-ray compared to drugs plus X-ray, resp., were: PC-3 prostate, 42-97; H-1579 prostate, 29-115; glioblastoma, 5-51; breast, 50-80; lung, 32-123. Comparative studies with PC-3 and H-1579 using CldC coadministered with H4U, showed that both PALA and FdC are dispensable, and the protocol can be simplified with equal and possibly heightened efficacy. For example, PC-3 with X-ray and (1) no drugs, (2) CldC plus the three modulators, (3) a high dose of CldC, and (4) escalating doses of CldC resulted in 0/10, 3/9, 5/10, and 6/9 cures, resp. The tumor regrowth delay data followed a similar pattern. After treating mice only 1 wk with CldC +H4U, 92% of the PC-3 tumor cells were found to possess CldU in their DNA. The great majority of head-and-neck tumors from patient material had markedly higher levels of dC kinase and dCMP deaminase than found in adjacent normal tissue. Physiol. and histol. studies showed that CldC +H4U combined with X-ray, focused on the cervical spinal cord, did not result in damage to that tissue. Conclusions: 5-CldC coadministered with only H4U is an effective radiosensitizer of human tumors. Ninety-two percent of PC-3 tumor cells have been shown to take up ClUra derived from CldC in their DNA after only 1 wk and 2 wk of bolus i.p. injections. Enzymic alterations that make tumors successful have been exploited for a therapeutic advantage. The great electronegativity, coupled with the relatively small Van der Waal radius of the Cl atom, may result in CldC possessing the dual advantageous properties of FdC on one hand and BrdU and IdU on the other hand. These advantages include autoenhancing the incorporation of CldUTP into DNA by not only overrunning but also inhibiting the formation of competing TTP pools in tumors. A clin. trial is about to begin, with head-and-neck tumors as a first target of CldC radiosensitization.

IT 32387-56-7, 5-Chlorodeoxycytidine  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
 (antitumor action mechanism of chlorodeoxycytidine alone or in combination with other radiosensitizers)

RN 32387-56-7 CAPLUS

CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER: 2000:628023 CAPLUS  
 DOCUMENT NUMBER: 133:219596  
 TITLE: Dramatic simplification of a method to treat  
 neoplastic disease by radiation  
 INVENTOR(S): Greer, Sheldon B.  
 PATENT ASSIGNEE(S): Halogenetics, Inc., USA  
 SOURCE: PCT Int. Appl., 54 pp.  
 CODEN: PIXXD2  
 DOCUMENT TYPE: Patent  
 LANGUAGE: English  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051639	A2	20000908	WO 2000-US2530	20000301
WO 2000051639	A3	20010111		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6933287	B1	20050823	US 2000-514278	20000228
EP 1156827	A2	20011128	EP 2000-911684	20000301
EP 1156827	B1	20060920		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY				
AT 339960	T	20061015	AT 2000-911684	20000301
ES 2273672	T3	20070516	ES 2000-911684	20000301
US 20040192639	A1	20040930	US 2004-779746	20040218
PRIORITY APPLN. INFO.:			US 1999-122479P	P 19990301
			US 2000-514278	A3 20000228
			WO 2000-US2530	W 20000301

AB The present invention is related to agents useful in the treatment of tumors by radiation by sensitizing tumor cells toward the radiation. The agents of the invention can perform selective tumor radiosensitization and be involved in tumor directed hypomethylation. The agents of the invention include (a) 5-chloro-2'-deoxycytidine (CldC) administered without a cytidine deaminase inhibitor, (b) CldC administered with a cytidine deaminase inhibitor, (c) CldC and 4-N-methylamino 5-fluoro-2'-deoxycytidine (4-N-methylamino FdC), or (d) CldC and 4-N-methylamino FdC coadministered with a cytidine deaminase inhibitor. The cytidine deaminase inhibitor can be tetrahydrouridine or Zebularine. Within the scope of the invention are methods of treating tumors by administering the agents of the present invention without the need of other modulators of metabolism. Another aspect of the invention is a method of hypomethylating a gene silenced in a tumor of a subject by administering the agents of the invention to the subject to reduce the aggressiveness of the tumor, the metastatic propensity of the tumor, the genetic instability of the tumor, and/or the resistance of the tumor to drug or radiation treatment. An addnl. aspect of the invention is a method of protecting normal tissues during a radiation treatment of a tumor in a subject by administering the agents of the invention to the subject before or during the radiation treatment. The agents of the invention can be combined with new sources or new schedules of radiation, and new categories of tumors can also be treated with the agents of the invention.

IT 32387-56-7, 5-Chloro-2'-deoxycytidine



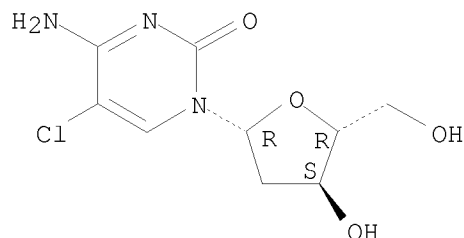
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(treating neoplastic disease by radiosensitization and tumor directed hypomethylation)

RN 32387-56-7 CAPLUS

CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1995:732651 CAPLUS

DOCUMENT NUMBER: 123:187874

ORIGINAL REFERENCE NO.: 123:33089a,33092a

TITLE: Five-chlorodeoxycytidine and biomodulators of its metabolism result in fifty to eighty percent cures of advanced EMT-6 tumors when used with fractionated radiation

AUTHOR(S): Greer, Sheldon; Schwade, James; Marion, H. Stan

CORPORATE SOURCE: Dep. Microbiol. Immunol., Univ. Miami Sch. Med., Miami, FL, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (1995), 32(4), 1059-69  
CODEN: IOBPD3; ISSN: 0360-3016

PUBLISHER: Pergamon

DOCUMENT TYPE: Journal

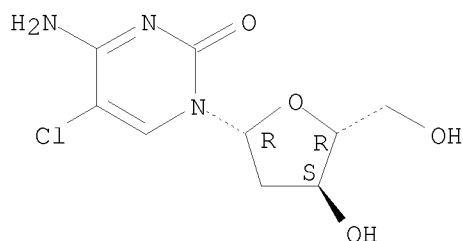
LANGUAGE: English

AB Purpose: to extend our findings in previous radiation and biochem. studies with five rodent tumors, in which we used one and occasionally two or three irradiations. The extent of control of the EMT-6 mammary adenocarcinoma was determined using fractionated radiation (12 irradiations) over a 3-wk period using the radiosensitizer 5-chloro-2'-deoxycytidine (CldC) and biomodulators of its metabolism: N-(phosphonacetyl)-L-aspartate (PALA), tetrahydrouridine and 5-fluoro-2'-deoxycytidine (FdC). Methods and Materials: mammary adenocarcinoma EMT-6 tumors implanted 1 wk prior to therapy in BALB/c mice were subjected to single daily doses of focused radiation, not exceeding a total of 60 Gy, on days 2-5 of each wk. PALA was administered on the first day of therapy. 5-Fluoro-2'-deoxycytidine and CldC were administered in the morning and afternoon, resp., of the next 2 days, and CldC was administered on the fourth day. Tetrahydrouridine was always coadministered with FdC or CldC. Drug and radiation treatments overlapped for 3 wks. Results: fifty to 80% cures (usually 70%) were obtained with no apparent morbidity and the same moderate weight loss that occurs with radiation alone. Neither tumor regrowth delay nor cures were obtained with drugs or radiation alone. An apparent threefold dose increase effect was obtained with the end point: "days to reach 4 times initial tumor volume". Increasing the radiation dose threefold (without drugs) resulted in four out of

five deaths; increasing the dose twofold (without drugs) resulted in extensive weight loss and hair loss in the entire ventral area and no cures. Increasing the dose of drugs or radiation 1.5-fold, in the complete protocol, did not result in increased morbidity. Comparative studies with Iododeoxyuridine demonstrate the heightened efficacy of CldC. Conclusions: one cannot achieve the same results obtained with CldC and the modulators by merely increasing the dose of radiation. There is a significant window of safety in this approach. The evidence we have obtained with EMT-6, the fifth rodent tumor we have studied with CldC, as well as the demonstrated and proposed reasons for its superior efficacy over 5-Iododeoxyuridine (and 5-Bromodeoxyuridine), drugs in current use, indicate that CldC will allow more aggressive treatment of human tumors with radiation than is now feasible.

IT 32387-56-7, 5-Chloro-2'-deoxycytidine  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(treatment of mammary adenocarcinoma with chlorodeoxycytidine and radiotherapy)  
RN 32387-56-7 CAPLUS  
CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2009 ACS on STN  
ACCESSION NUMBER: 1992:190295 CAPLUS  
DOCUMENT NUMBER: 116:190295  
ORIGINAL REFERENCE NO.: 116:32131a,32134a  
TITLE: 5-Chlorodeoxycytidine, a radiosensitizer effective against RIF-1 and Lewis lung carcinoma, is also effective against a DMBA-induced mammary adenocarcinoma and the EMT-6 tumor in BALB/c mice  
AUTHOR(S): Greer, Sheldon; Santos, Orlando; Gottlieb, Charles; Schwade, James; Marion, H. Stan  
CORPORATE SOURCE: Sch. Med., Univ. Miami, Miami, FL, 33136, USA  
SOURCE: International Journal of Radiation Oncology, Biology, Physics (1992), 22(3), 505-10  
CODEN: IOBPD3; ISSN: 0360-3016  
DOCUMENT TYPE: Journal  
LANGUAGE: English  
AB 5-Chlorodeoxycytidine (CldC), coadministered with modulators of pyrimidine metabolism, is an effective radiosensitizer of murine tumors. Past studies that utilized RIF-1 tumors in C3H mice and Lewis lung carcinoma (LLC) in BDF1 mice have been extended with an emphasis on using multiple cycles of drug administration followed by irradiation of LLC and the use of two addnl. tumor models. Four of 7 cures of BDF1 mice bearing LLC were obtained with 3 doses of 20 Gy irradiation, in which the first and third dose were preceded by a "Standard Protocol" that includes N-(phosphonacetyl)-L-aspartic acid (PALA), 5-fluorodeoxycytidine (FdC), tetrahydrouridine, and the radiosensitizer, 5-chlorodeoxycytidine. No cures were obtained in groups of mice receiving radiation alone or drugs alone, and there were

no "no takes" in untreated control groups (6 mice/group). Extensive tumor inhibition, exceeding that obtained with drugs or radiation alone, was obtained with 2 cycles of drugs and radiation combined when a dimethylbenzanthracene-induced mammary adenocarcinoma was used in BALB/c mice. With the EMT-6 tumor in BALB/c mice, doses of 10 and 20 Gy were administered 9 and 16 days after tumor implantation, each preceded with the Standard Protocol; this resulted in a tumor growth delay of 24 days. No tumor growth delay occurred with drugs or radiation alone. The omission of PALA, FdC or CldC from the Standard Protocol resulted in loss of tumor control, which was obtained with the complete protocol. The fact that 5-chlorodeoxycytidine is an effective radiosensitizer in 4 rodent tumor systems is compelling evidence that it has potential as a radiosensitizer of human tumors, especially in view of its tumor selectivity

and

its resistance to catabolism when used with modulators of its metabolism, and in view of the high levels of the key enzymes in human tumors, which can convert 5-chlorodeoxycytidine to 5-chlorodeoxyuridine triphosphate, the proximate radiosensitizer.

IT 32387-56-7, 5-Chlorodeoxycytidine

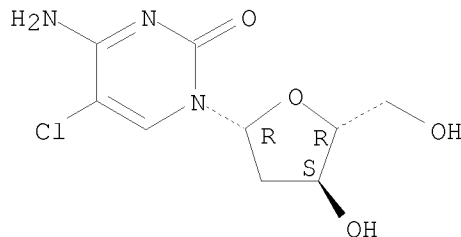
RL: BIOL (Biological study)

(radiosensitizer, for lung carcinoma and mammary adenocarcinoma)

RN 32387-56-7 CAPLUS

CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1988:2749 CAPLUS

DOCUMENT NUMBER: 108:2749

ORIGINAL REFERENCE NO.: 108:547a,550a

TITLE: Potentiation of halogenated pyrimidine  
radiosensitizers in human carcinoma cells by  
 $\beta$ -lapachone

(3,4-dihydro-2,2-dimethyl-2H-naphtho[1,2-b]pyran-5,6-dione), a novel DNA repair inhibitor

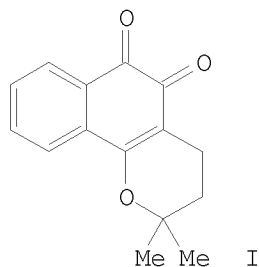
AUTHOR(S): Boothman, David A.; Greer, Sheldon; Pardee, Arthur B.  
CORPORATE SOURCE: Dana Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA

SOURCE: Cancer Research (1987), 47(20), 5361-6  
CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB  $\beta$ -Lapachone (I) is a novel DNA repair inhibitor. It was tested for synergistic x-ray-induced lethality in combination with several halogenated pyrimidine radiosensitizers. Logarithmic-phase growing human epidermoid laryngeal carcinoma (HEp-2) cells were allowed to incorporate pyrimidine analogs for 48 h (.apprx.2 cell doublings) and then were x-irradiated and subjected to various posttreatments. I synergistically increased the dose enhancement ratios (DERs) of all analogs screened, with the exception of the 2'-chloro derivative of 5-bromodeoxyuridine. For example, following 5-bromodeoxycytidine sensitization, an x-ray DER value of 1.87 at 1% survival was increased to 3.51 due to a 4-h post-x-irradiation exposure to 4  $\mu$ M I. Do (Mean LD) and Dq (quasi-threshold dose) values for halogenated pyrimidine-sensitized human epidermoid laryngeal carcinoma cells were decreased 1.4-5.4-fold and 1.4-4.0-fold, resp. I had little effect upon the cytotoxicities of unirradiated human epidermoid laryngeal carcinoma cells whether or not they were previously exposed to any of the halogenated pyrimidine radiosensitizers. I treatment following x-irradiation of cell that had not incorporated a pyrimidine analog exhibited DER values of 1.38 and 1.40 at 10 and 1% survival levels, resp. I enhanced the radiosensitization of deoxycytidine analog to a greater extent than the structurally related deoxyuridine analogs. Greater DERs and lower Do and Dq values were found for deoxycytidine than for deoxyuridine analog radiosensitizers following I treatment. This agent may improve presently used radiation therapies and enhance proposed strategies which utilize deoxycytidine analog radiosensitization together with protection of normal tissues by tetrahydrouridine to achieve tumor-selective radiotherapy.

IT 32387-56-7, 5-Chloro-2'-deoxycytidine

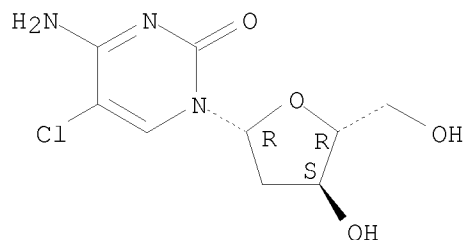
RL: BIOL (Biological study)

(radiosensitization by, of human carcinoma cells x-rays, lapachone potentiation of)

RN 32387-56-7 CAPLUS

CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



ORIGINAL REFERENCE NO.: 105:6285a,6288a  
TITLE: In vitro and in vivo radiation sensitization  
by the halogenated pyrimidine  
5-chloro-2'-deoxycytidine  
AUTHOR(S): Russell, Kenneth J.; Rice, Glenn C.; Brown, J. Martin  
CORPORATE SOURCE: Med. Cent., Stanford Univ., Stanford, CA, 94305, USA  
SOURCE: Cancer Research (1986), 46(6), 2883-7  
CODEN: CNREA8; ISSN: 0008-5472

DOCUMENT TYPE: Journal  
LANGUAGE: English

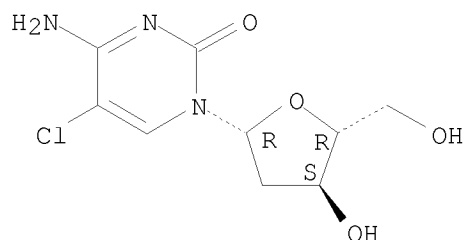
AB 5-Chloro-2'-deoxycytidine (Cld/Cyd) is hypothesized to have preferential incorporation into tumor DNA on the basis of elevated deoxycytidine-5'-phosphate deaminase and deoxycytidine kinase levels in tumors. Radiosensitization by Cld/Cyd was evaluated in exponentially growing Chinese hamster ovary cells by determining the ratio of radiation doses in control and treated cells to produce the same degree of cell killing (sensitizer enhancement ratio). Sensitizer enhancement ratios of 1.2-1.8 are seen at Cld/Cyd concns. of 3-100  $\mu$ M, 64 h incubation, and 200-600 cGy x-irradiation. Coincubation with tetrahydrouridine (H4Urd), a proposed inhibitor of Cld/Cyd catabolism by plasma cytidine deaminase, resulted in no enhanced drug or radiation cytotoxicity. C3H mice given implants of RIF-1 tumors received 72-h continuous i.p. infusions of Cld/Cyd with or without H4Urd, or 5-bromo-2'-deoxyuridine (BrdUrd). Excised tumors were irradiated as single cell suspensions in vitro. Infusions of equimolar (0.4 mmol/kg/day) Cld/Cyd or BrdUrd resulted in greater radiosensitization by BrdUrd with no potentiation of Cld/Cyd by coinfusion with 0.8 mmol/kg/day H4Urd. Infusions with equitoxic doses of Cld/Cyd (0.8 mmol/kg/day) or BrdUrd (0.4 mmol/kg/day) yielded equal BrdUrd and Cld/Cyd sensitizer enhancement ratios of 1.6, without H4Urd potentiation of Cld/Cyd. Fluorescence-activated cell sorter anal. of tumor cell suspensions using a monoclonal antibody reactive with BrdUrd and Cld/Cyd disclosed a population of noncycling cells in tumors treated with Cld/Cyd/H4Urd that is not seen in tumors exposed to either BrdUrd or Cld/Cyd alone.

IT 32387-56-7  
RL: BIOL (Biological study)  
(radiosensitization by, of CHO cells and neoplasms)

RN 32387-56-7 CAPLUS

CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1985:476273 CAPLUS

DOCUMENT NUMBER: 103:76273

ORIGINAL REFERENCE NO.: 103:12215a,12218a

TITLE: Method and materials for sensitizing neoplastic tissue  
to radiation

INVENTOR(S): Greer, Sheldon B.

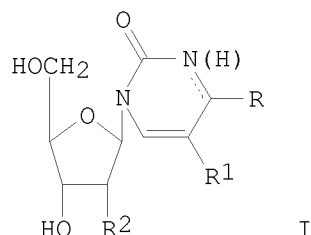
PATENT ASSIGNEE(S): USA

SOURCE: PCT Int. Appl., 31 pp.

CODEN: PIXXD2  
DOCUMENT TYPE: Patent  
LANGUAGE: English  
FAMILY ACC. NUM. COUNT: 1  
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8501871	A1	19850509	WO 1984-US1735	19841026
W: AU, BR, DK, FI, JP, US				
RW: AT, BE, CH, DE, FR, GB, LU, NL, SE				
AU 8436107	A	19850522	AU 1984-36107	19841026
AU 583801	B2	19890511		
EP 160079	A1	19851106	EP 1984-904049	19841026
EP 160079	B1	19900131		
R: AT, BE, CH, DE, FR, GB, LI, LU, NL, SE				
JP 61500224	T	19860206	JP 1984-504070	19841026
JP 05086376	B	19931210		
AT 49894	T	19900215	AT 1984-904049	19841026
US 4894364	A	19900116	US 1985-749540	19850624
CA 1269658	A1	19900529	CA 1985-494396	19851101
PRIORITY APPLN. INFO.:			US 1983-545693	A2 19831026
			EP 1984-904049	A 19841026
			WO 1984-US1735	A 19841026

GI



AB I (R = NH<sub>2</sub> or O, R<sub>1</sub> and R<sub>2</sub> = H or halogen) for use in pharmaceutical compns. are radiosensitizers. The concentration of the active ingredient in the

composition is 0.01-25% by weight depending on the route of administration, severity of the case, frequency of administration, etc. The radiation dose, x- or γ-ray will be either the same or one-fourth to three-fourths the dose given to patients not receiving the pretreatment sensitizer, and this will result in either a more effective tumor kill or an equal tumor kill but with less damage to underlying tissues. In a toxicity study in animals injected i.p. with N-(phosphonoacetyl)-L-aspartate [51321-79-0] (pretreatment agent) 200, followed 24 h later with i.p. 5-fluoro-2'-deoxyuridine (I; R = NH<sub>2</sub>, R<sub>1</sub> = F, R<sub>2</sub> = H) [50-91-9] 50, and 4 h later i.p. 5-chloro-2'-deoxycytidine (I; R = NH<sub>2</sub>, R<sub>1</sub> = Cl, R<sub>2</sub> = H) [32387-56-7] 500 coadministered with tetrahydrouridine [18771-50-1] 100 mg, the last 2 compds. administered at the same concentration twice at 10 h intervals, a 4% weight

loss

occurred which is trivial compared to normal weight loss which occurs from administration of antitumor agents in radiation therapy.

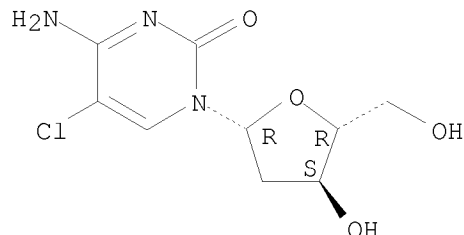
IT 32387-56-7

RL: BIOL (Biological study)  
(radiosensitizer composition containing)

RN 32387-56-7 CAPLUS

CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1984:625942 CAPLUS

DOCUMENT NUMBER: 101:225942

ORIGINAL REFERENCE NO.: 101:34219a,34222a

TITLE: Marked radiosensitization of cells in culture to x-ray by 5-chlorodeoxycytidine coadministered with tetrahydrouridine, and inhibitors of pyrimidine biosynthesis

AUTHOR(S): Perez, Liliana M.; Mekras, John A.; Brigggle, Thomas V.; Greer, Sheldon

CORPORATE SOURCE: Sch. Med., Univ. Miami, Miami, FL, 33101, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (1984), 10(8), 1453-8  
CODEN: IOBPD3; ISSN: 0360-3016

DOCUMENT TYPE: Journal

LANGUAGE: English

AB To overcome the problem of rapid catabolism and general toxicity encountered with 5-halogenated analogs of deoxyuridine (5-bromo, chloro, or iododeoxyuridine), which has limited their use as tumor radiosensitizers, 5-chlorodeoxycytidine (CldC) with tetrahydrouridine (H4U) is utilized. In x-irradiation studies with HEP-2 cells, limited to 1 or 2 radiation doses, 3.0-3.8 apparent dose enhancement ratios (these represent upper limits) were obtained when cells are preincubated with inhibitors of pyrimidine biosynthesis, i.e., N-(phosphonacetyl)-L-aspartate (PALA) and 5-fluorodeoxyuridine (FdU) or 5-fluorodeoxycytidine (FdC) + H4U. Optimum conditions for radiosensitization are PALA (0.1 mg/mL) 18-20 h prior to FdU (0.1  $\mu$ M) or FdC (0.02  $\mu$ M) + H4U (0.1 mM) followed 6 h later by CldC (0.1-0.2 mM) + H4U (0.1 mM) for 56-68 h. Viabilities of 10-15% were obtained for drug-treated unirradiated cells. Enzymic studies indicate that this toxicity may be tumor selective. CldC + H4U alone (at these concns.) results in 20% substitution of CldU for thymidine in DNA (determined by HPLC anal.). Preliminary toxicity studies indicate that mice will tolerate treatment protocols involving a single dose of PALA (200 mg/kg) followed by a dose of FdU (50 mg/kg) and 3 cycles of CldC (500 mg/kg) + H4U (100 mg/kg) at 10 h intervals, with marginal weight loss (4%). In this approach, preferential conversion of CldC to CldUTP at the tumor site is obtained by taking advantage of quant. differences in enzyme levels between tumors and normal tissues.

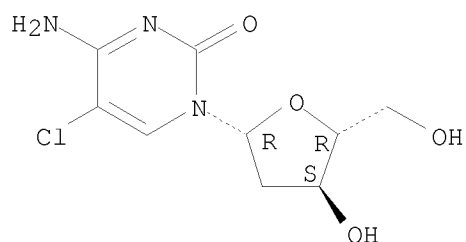
IT 32387-56-7

RL: BIOL (Biological study)  
(radiosensitization by tetrahydrouridine coadministration with, of cells in culture)

RN 32387-56-7 CAPLUS

CN Cytidine, 5-chloro-2'-deoxy- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 18 OF 20 USPATFULL on STN

ACCESSION NUMBER: 2005:211182 USPATFULL

TITLE: Dramatic simplification of a method to treat neoplastic disease by radiation

INVENTOR(S): Greer, Sheldon B., 3600 Mystic Pointe Dr., LPH9, Aventura, FL, UNITED STATES 33180

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6933287	B1	20050823
APPLICATION INFO.:	US 2000-514278		20000228 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-122479P	19990301 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	GRANTED	
PRIMARY EXAMINER:	Cook, Rebecca	
LEGAL REPRESENTATIVE:	Rothwell, Figg, Ernst & Manbeck, P.C.	
NUMBER OF CLAIMS:	20	
EXEMPLARY CLAIM:	1	
NUMBER OF DRAWINGS:	5 Drawing Figure(s); 3 Drawing Page(s)	
LINE COUNT:	1518	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of treating tumors with radiation is disclosed, wherein the tumor is sensitized by administering a tumor sensitizing agent comprising 5-chloro-2'-deoxycytidine, 4-N-methyl FdC and a cytidine deaminase inhibitor to a patient having the tumor. The tumor is then subjected to radiation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 19 OF 20 USPATFULL on STN

ACCESSION NUMBER: 2004:248039 USPATFULL

TITLE: Dramatic simplification of a method to treat neoplastic disease by radiation

INVENTOR(S): Greer, Sheldon B., Miami, FL, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040192639	A1	20040930
APPLICATION INFO.:	US 2004-779746	A1	20040218 (10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2000-514278, filed on 28 Feb 2000, PENDING		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-122479P	19990301 (60)
DOCUMENT TYPE:	Utility	



FILE SEGMENT: APPLICATION  
LEGAL REPRESENTATIVE: ROTHWELL, FIGG, ERNST & MANBECK, P.C., 1425 K STREET,  
N.W., SUITE 800, WASHINGTON, DC, 20005  
NUMBER OF CLAIMS: 21  
EXEMPLARY CLAIM: 1  
NUMBER OF DRAWINGS: 3 Drawing Page(s)  
LINE COUNT: 1438

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method of treating tumors with radiation is disclosed,  
wherein the tumor is sensitized by administering a tumor sensitizing  
agent comprising 5-chloro-2'-deoxycytidine, 4-N-methyl FdC and a  
cytidine deaminase inhibitor to a patient having the tumor. The tumor is  
then subjected to radiation.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 20 OF 20 USPATFULL on STN  
ACCESSION NUMBER: 90:4372 USPATFULL  
TITLE: Method and materials for sensitizing neoplastic tissue  
to radiation  
INVENTOR(S): Greer, Sheldon B., 8320 SW 86 Ter., Miami, FL, United  
States 33143

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 4894364		19900116
	WO 8501871		19850509
APPLICATION INFO.:	US 1985-749540		19850624 (6)
	WO 1984-US1735		19841026
			19841026 PCT 371 date
			19010101 PCT 102(e) date
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. US 1983-545693, filed on 26 Oct 1983, now abandoned		
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	Granted		
PRIMARY EXAMINER:	Lilling, Herbert J.		
LEGAL REPRESENTATIVE:	Armstrong, Nikaido, Marmelstein, Kubovcik & Murray		
NUMBER OF CLAIMS:	11		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	14 Drawing Figure(s); 7 Drawing Page(s)		
LINE COUNT:	640		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Tumors are sensitized to radiation by administration of  
5-chlorodeoxycytidine (5-CldC) or 5-halo-2'-halo-2'-deoxy-cytidine or  
-uridine derivatives. Tetrahydrouridane (H.sub.4 U) and/or  
2'-deoxytetrahydrouridine (dH.sub.4 U) is preferably coadministered with  
the deoxycytidine derivative to inhibit deamination of the deoxycytidine  
derivatives. Optional pre- or concurrent treatment with agents to reduce  
the amount of competing metabolites to favor CldC, such as  
5-fluorodeoxyuridine, results in a procedure that significantly  
increases the dose effects of X-radiation. Pharmaceutical  
compositions suitable for the sensitization of tumors to  
radiation are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d his

(FILE 'HOME' ENTERED AT 13:49:17 ON 31 MAR 2009)

FILE 'REGISTRY' ENTERED AT 13:49:29 ON 31 MAR 2009

E "5-CLDC"/CN 25  
E "CLDC"/CN 25  
E "5-CHLORO-2-DEOXYCYTIDINE"/CN 25  
E "CHLORO-2-DEOXYCYTIDINE"/CN 25  
E "5-CHLORO-2'-DEOXYCYTIDINE"/CN 25

L1 1 S E3

FILE 'MEDLINE, CAPLUS, WPIDS, USPATFULL' ENTERED AT 13:51:15 ON 31 MAR 2009

L2 59 S L1  
L3 26 S L2 AND TETRAHYDROURIDINE  
L4 20 S L3 AND RADIATION

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE	TOTAL
	ENTRY	SESSION
FULL ESTIMATED COST	74.53	83.59
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE	TOTAL
	ENTRY	SESSION
CA SUBSCRIBER PRICE	-7.38	-7.38

STN INTERNATIONAL LOGOFF AT 13:54:38 ON 31 MAR 2009